REMARKS

Reconsideration is respectfully requested.

Claim 2 is reiterated. Claims 1-3 and 5 has been amended. Claims 6-28 have been added. Upon entry of this amendment, claims 1-26 will be pending.

Claims 1 and 4 have been amended to include a cleavable linker between biotin and UTP. Support for the amendment may be found, for example, at page 21, lines 1-11 and page 65, Example 18.

Claim 3 has been amended to depend from claim 1, as amended.

Claim 5 has been amended to depend from a "method" claim. Claim 5 originally depended from claim 4, directed to a kit.

Claims 6-27 have been added. Support for claim 6 may be found, for example, at page 4, line 17-28. Support for a "solid matrix" may be found, for example, at page 27 lines 17-26 of the specification. Support for cleavable linkers and disulfide cleavable linkers may be found, for example, at page 21 lines 1-11 and page 65, Example 18. Support for claim 17 may be found, for example, at page 5, lines 1-17 of the specification. Support for claims 18 may be found, for example, at page 5, lines 18-31 of the specification. Support for claim 19 may be found, for example, at page 67 line 1 through page 68 line 22. Support for claim 20 may be found, for example, at page 68, line 24, though page 70, line 24. Support for claim 21 may be found, for example, at page 5 lines 1-15. Support for claims 22-27 may be found at page 23 line 27 through page 26, line 28 and page 28 line 10 through page 29 line 2.

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications. The amendment herein only makes explicit what was already implicit in the claims.

Petition to Make Special

Applicants acknowledge that Applicants' petition to make special was granted on September 20, 2002.

Specification

The Examiner has noted that the uses of numerous trademarks, including Dynabeads (page 20, line 25), in the Application. Applicants further note that the Examiner has not objected to the Specification.

Applicants note that the term "Dynabeads" is capitalized throughout the specification to reflect its trademarked status.

Claim Rejections - 35 U.S.C. §112, first paragraph – Written Description

The Examiner has rejected claims 3 and 5 under 35 U.S.C. §112, first paragraph.

Claims 3 and 5

Claim 3 recites "the method of Claim 1, wherein the RNA transcripts are eluted from the iron beads prior to the quantitative determination." Claim 5 recites "the method of Claim 2, wherein the RNA transcripts are eluted from the iron beads prior to the quantitative determination."

The Examiner's Rejection

The Examiner alleges that claims 3 and 5 contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner admits that "at the top of page 21 the specification states the 'the present invention further proposes to modify Dynabead immobilization to enable labeled transcripts to be cleaved or eluted off the bead by the incorporation of a cleavable or otherwise labile linker between, for example, a UTP and a biotin label or between a Dynabead and strepatavidin'." The Examiner further admits that "example 18 (page 65, first paragraph) states that the 'process *is* modified to enable the streptavadin Dynabead captured biotin UTP labeled transcripts to be cleaved or eluted.'" (*emphasis added*).

In spite of the Examiner's admissions, the Examiner asserts the "the specification does not demonstrate that such a modification was made by the applicants or that the modification allowed elution of the captured RNA."

The Written Description Requirement

The MPEP provides specific guidelines for examination of patent applications under the 35 U.S.C. §112, first paragraph written description requirement. *See* MPEP §2163. To satisfy the written description requirement, a patent specification must describe the claimed invention in

sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." Further, the MPEP points out that "a description as filed is *presumed to be adequate* unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption." (MPEP §2163 III. A., *emphasis added*). Moreover, "it is now well accepted that a satisfactory description may be *in the claims* or *any other portion* of the originally filed specification." (MPEP §2163, I, *emphasis added*). "There is a *strong presumption* that an adequate written description of the claimed invention is present when the application is filed." (MPEP §2163 I. A., citing *In re Wertheim*, 541 F.2d 257, 263 (CCPA 1976)).

Applicant's Response

Applicants respectfully traverse this rejection, since the Examiner did not meet the requisite *prima facie* burden of providing a reasonable basis to challenge the adequacy of the written description. Moreover, the Examiner failed to articulate evidence or reasoning to overcome the strong presumption of the adequacy of the written description in the specification, including the originally filed claims.

Applicants respectfully point out that the Examiner has not satisfied the *prima facie* burden of overcoming the "strong presumption" of a sufficient written description in the specification and originally filed claims. First, Applicants have provided a description of the methods in claims 3 and 5 in the Detailed Description. As noted by the Examiner, the Specification states the "process *is* modified to enable the streptavadin Dynabead captured biotin UTP labeled transcripts to be cleaved or eluted" (Specification, Example 18, Page 65, *emphasis added*). This is a statement of what actually *is*, not a statement of what could or might exist. Second, Applicants have provided a description in the originally filed claims. *Original claims* 3 and 5 state "the biotin-labeled RNA transcripts *are* eluted from the iron beads prior to the quantitative determination." (*Emphasis added*). Neither statement is an assertion of what "could be," as alleged by the Examiner. Again, they are assertions of what *is*.

The Examiner hardly provides reasoning to overcome Applicant's presumption. The Examiner instead states, in conclusory fashion, that "*despite* [Applicant's] assertions..., the specification does not demonstrate that such a modification was made or that the modification allowed elution of the captured RNA." Applicants respectfully point out that they are not

required to provide examples of every claim limitation; a written description, as provided and discussed above, is sufficient.

The Examiner has failed to provide evidence or reasoning necessary to overcome the strong presumption that Applicants have provided an adequate written description of the subject matter of original claims 3 and 5. The Examiner has therefore failed to meet his *prima facie* burden. Applicants respectfully request that this ground for rejection be withdrawn.

Claim Rejections - 35 U.S.C. §102(a)

The Examiner has rejected claims 1 and 2 under 35 U.S.C. §102(a) as being anticipated by Patrone et al.

Claims 1, 2, 6, and 8

Claim 1 recites "a method for determining the rate of transcription of a transcriptional unit in a composition of cells, said method comprising:

lysing the cells and obtaining from the cells a preparation of nuclei comprising said transcriptional unit with nascent RNA strands attached thereto and placing same on ice to temporarily inhibit continued transcription and then placing said nuclei under conditions to permit transcription of the transcriptional unit in the presence of biotin-16-UTP to thereby provide a population of biotin-labeled nascent transcripts; and

isolating said biotin-labeled nascent transcripts by immobilizing same onto streptavidin-labeled iron beads and purifying same by magnetic separation and quantitatively determining the level of specific biotin-labeled RNA transcripts by subjecting the biotin-labeled RNA transcripts to real-time PCR."

Claim 2 recites "the method of claim 1 wherein the cells are mammalian cells."

Claim 6 recites "method for determining the rate of transcription of one or more transcriptional units in one or more cells, said method comprising:

obtaining from said one or more cells a preparation of nucleic acids comprising said one or more transcriptional units with nascent RNA strands attached thereto,

inhibiting continued transcription of said nucleic acids,

placing said nucleic acids under conditions to permit transcription of said transcriptional unit in the presence of biotin-labeled ribonucleotides, wherein said biotin-labeled ribonucleotides include a cleavable linker between said biotin and said ribonucleotide, to thereby provide a

population of biotin-labeled nascent RNA transcripts that include a cleavable linker between said biotin and said ribonucleotide;

isolating said biotin-labeled nascent transcripts by immobilizing said label onto a solid matrix,

cleaving said biotin-labeled ribonucleotide at said cleavable linker to thereby provide a population of nascent RNA transcripts;

and subjecting said nascent RNA transcripts to a real-time polymerase chain reaction to determine the rate of transcription of said one or more transcriptional units."

Claim 8 recites "a method for determining the rate of transcription of one or more transcriptional units in one or more cells, said method comprising:

obtaining from said one or more cells a preparation of nucleic acids comprising said one or more transcriptional units with nascent RNA strands attached thereto,

inhibiting continued transcription of said nucleic acids,

placing said nucleic acids under conditions to permit transcription of said transcriptional unit in the presence of biotin-labeled ribonucleotides to thereby provide a population of biotin-labeled nascent RNA transcripts;

isolating said biotin-labeled nascent transcripts by immobilizing said label onto a solid matrix, wherein said matrix includes a cleavable linker;

cleaving said matrix at said cleavable linker to thereby provide a population of biotin-labeled nascent RNA transcripts;

and subjecting said biotin-labeled nascent RNA transcripts to a real-time polymerase chain reaction to determine the rate of transcription of said one or more transcriptional units."

The Cited Reference

Patrone et al. disclose a method for determining the rate of transcription by a modified run-on assay that captures biotin-labeled ribonucleotides on streptavidin coated beads. Patrone, however, is devoid of any teaching or suggestion of a cleavable linker, or a step of cleaving the cleavable linker, as required by the claims.

The Examiner's Rejection

The Examiner alleges that Patrone "includes all the steps of the instant application: lysing cells, purifying nuclei, and putting the nuclei on ice (page 1014, left column, second paragraph)

incubating the nuclei under conditions that allow transcription of RNA in the presence of biotin-16-UTP (page 1014, left column, third paragraph), immobilizing the biotin-labeled RNA transcripts onto streptavidin-coated beads (page 1012, right column, third paragraph), purifying the transcripts by magnetic separation of the beads from the solution (page 1014, left column, last paragraph), and quantitative PCR of specific RNA transcripts (page 1014, center column, second paragraph." The Examiner does not state that the Patrone reference includes any mention of a cleavable linker, either between biotin and the ribonucleotide, or included in the solid matrix.

The Cited Reference Distinguished

In order to anticipate under 35 U.S.C. §102, every element of the claimed invention must be identically shown in a single reference. *In re Bond,* 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990). The Patrone reference fails to anticipate the claims, since the reference fails to teach multiple elements of the claims.

Specifically, Patrone et al. fail to disclose a cleavable linker, or a step of cleaving the cleavable linker, as required by the claims. The claims as amended include a cleavable linker, either between the biotin and ribonucleotides, or in the solid matrix. This limitation is not found anywhere in the Patrone reference. Further, the claims include a step of cleaving the cleavable linker prior to subjecting the nascent RNA transcripts or biotin-labeled transcripts to real-time PCR.

Since Patrone et al. fails to teach every claim limitation, Patrone et al. fail to anticipate the claims under 35 U.S.C. §102(b). Applicants respectfully request that this ground for rejection be withdrawn.

Claim Rejections - 35 U.S.C. §103(a)

A. Rejection of Claims 4 and 5 over Patrone et al.

The Examiner has rejected claims 4 and 5 under 35 U.S.C. §103(a) as being obvious over Patrone et al.

Claims 4 and 5

Claim 4 is directed to a kit.

Claim 5 has been amended to depend from method claim 2, not kit claim 1.

Claim 22 is directed to "a kit for determining the rate of transcription of a transcriptional unit in one or more cells, said kit comprising: enzymes, buffers, and diluents for obtaining

nucleic acids; biotin-labeled ribonucleotides, wherein said biotin-labeled ribonucleotides include a cleavable linker between said biotin and said ribonucleotide; enzymes, buffers, and diluents for transcription of nucleic acids; a solid matrix; enzymes, buffers, and diluents for isolating biotin-labeled molecules using said solid matrix; and enzymes, buffers, and diluents for real time polymerase chain reaction."

Claim 23 is directed to "a kit for determining the rate of transcription of a transcriptional unit in one or more cells, said kit comprising: enzymes, buffers, and diluents for obtaining nucleic acids; biotin-labeled ribonucleotides; enzymes, buffers, and diluents for transcription of nucleic acids; a solid matrix, wherein said matrix includes a cleavable linker; enzymes, buffers, and diluents for isolating biotin-labeled molecules using said solid matrix, wherein said matrix includes a cleavable linker; and enzymes, buffers, and diluents for real time polymerase chain reaction."

The Cited Reference

Patrone et al. disclose a method for determining the rate of transcription in by a modified run-on assay involving capturing biotin-labeled ribonucleotides on streptavidin coated beads. Patrone, however, is devoid of any teaching or suggestion of a cleavable linker, or a step of cleaving the cleavable linker, as required by the claims.

The Examiner's Rejection

The Examiner argues that Patrone et al. teach a method of using the compounds of the kits. The Examiner further argues that kits are known in the art, and that it would have been obvious to make a kit including components used in a known method.

The Cited Reference Distinguished

35 U.S.C. § 103(a) requires that "differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). The prima facie case must satisfy three requirements: 1) the references must teach or suggest all the claim limitations; 2) the prior art combined with general knowledge must include a suggestion or incentive to modify or combine the references; and 3) the modification or combination must have a reasonable chance of success.

1. The reference must teach or suggest all claim limitations

First, Patrone et al. fail to disclose all claim limitations of the invention. Specifically, Patrone et al. fail to teach or suggest a cleavable linker, or cleaving the cleavable linker, as required by the claims. In addition, Patrone et al. fail to teach or suggest a kit. Since these limitations are not taught or suggested in the cited reference, the reference relied on by the Examiner fail to meet every claim limitation.

2. Motivation or Suggestion to Combine

Second, Patrone et al. fail to provide the requisite motivation or suggestion to include a cleavable linker in biotin ribonucleotide or the matrix, or to put the compositions disclosed in Patrone in a kit.

As pointed out above, the claims require that the kit include a cleavable linker either between the biotin and ribonucletide or in the solid matrix. Patrone et al. fail to include this limitation. Further, Patrone et al. fail to teach, suggest, or hint that the method may be modified to include a cleavable linker. The reference also fails to disclose a kit, or provide a motivation or suggestion to make a kit including the claimed components. Since there is no motivation or suggestion of cleavable linkers, and, indeed, no mention of a cleavable linker in the first place, the cited reference fails to provide the requisite motivation or suggestion to modify the teaching of Patrone et al.

3. Reasonable Expectation of Success

Third, Patrone et al. fail to provide the requisite reasonable expectation of success to include a cleavable linker in biotin ribonucleotide or the matrix, or to put the compositions disclosed in Patrone in a kit.

As pointed out above, the claims require that the kit include a cleavable linker either between the biotin and ribonucletide or in the solid matrix. Patrone et al. fail to disclose, suggest, or hint at this limitation. Since Patrone et al. fail to even hint at this limitation, Patrone et al. therefore also fail to provide any possibility that one of ordinary skill in the art could reasonably expect to succeed in including a cleavable linker. Further, the reference fails to disclose a kit, or provide a reasonable expectation of success in making a kit including the claimed components. The reference thus fails to provide the requisite reasonable expectation of success in modifying the teachings of Patrone et al.

4. Official Notice

Concerning whether kits may be made to include components of methods such as those disclosed in Patrone et al., the Examiner fails to cite a reference that provides the limitation, motivation to combine the limitation, and that the limitation has a reasonable expectation of success. The Examiner appears to take official notice of these requirements of *prima facie* obviousness based on facts outside the record. Applicants respectfully traverse this assertion, and invite the Examiner to cite a reference in support of this position.

Since Patrone et al. fails to teach every claim limitation, provide a motivation or suggestion to modify the methods, and provide a reasonable expectation of success in modifying the methods, Patrone fails to render the claims obvious under 35 U.S.C. §103.

Applicants respectfully request that this ground for rejection be withdrawn.

B. Rejection of Claims 3 and 5 over Patrone et al.

The Examiner has rejected claims 3 and 5 under 35 U.S.C. §103(a) as being obvious over Patrone et al.

Claims 1, 3 and 5

Claim 1 recites "a method for determining the rate of transcription of a transcriptional unit in a composition of cells, said method comprising:

lysing the cells and obtaining from the cells a preparation of nuclei comprising said transcriptional unit with nascent RNA strands attached thereto and placing same on ice to temporarily inhibit continued transcription and then placing said nuclei under conditions to permit transcription of the transcriptional unit in the presence of biotin-16-UTP to thereby provide a population of biotin-labeled nascent transcripts; and

isolating said biotin-labeled nascent transcripts by immobilizing same onto streptavidin-labeled iron beads and purifying same by magnetic separation and quantitatively determining the level of specific biotin-labeled RNA transcripts by subjecting the biotin-labeled RNA transcripts to real-time PCR."

Claim 3, which depends from claim 1, recites "the method of Claim 1 wherein the RNA transcripts are eluted from the iron beads prior to the quantitative determination."

Claim 5, which depends from claim 1, recites "the method of Claim 1 wherein the biotin-labeled RNA transcripts are eluted from the iron beads prior to the quantitative determination."

The Cited Reference

As discussed previously and reiterated here, Patrone et al. disclose a method for determining the rate of transcription in by a modified run-on assay involving capturing biotin-labeled ribonucleotides on streptavidin coated beads. Patrone, however, is devoid of any teaching or suggestion of a cleavable linker, or a step of cleaving the cleavable linker, as required by claims 3 and 5.

The Examiner's Rejection

The Examiner has rejected claims 3 and 5, both of which depend from claim 1, as obvious over Patrone et al. The Examiner argues that eluting the RNA transcripts from iron beads is obvious to one of skill in the art.

The Cited Reference Distinguished

35 U.S.C. § 103(a) requires that "differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). The prima facie case must satisfy three requirements: 1) the references must teach or suggest all the claim limitations; 2) the prior art combined with general knowledge must include a suggestion or incentive to modify or combine the references; and 3) the modification or combination must have a reasonable chance of success.

1. The reference must teach or suggest all claim limitations

First, Patrone et al. fails to disclose all claim limitations of the invention. Claims 3 and 5, both of which depend from claim 1, require that the reference teaches a a cleavable linker, or cleaving the cleavable linker. Patrone et al., however, fails to teach or suggest a cleavable linker, or cleaving the cleavable linker, as required by the claims. Since this limitation is not taught or suggested in the cited reference, the reference relied on by the Examiner fail to meet every claim limitation.

2. Motivation or Suggestion to Combine

Second, Patrone et al. fail to provide the requisite motivation or suggestion to include a cleavable linker between the biotin and ribonucleotide, or in the matrix.

As pointed out above, the claims require that a cleavable linker either between the biotin and ribonucletide or in the solid matrix. Patrone et al. fail to include this limitation. Further, Patrone et al. fail to teach, suggest, or hint that the method may be modified to include a

cleavable linker. Since there is no motivation or suggestion of cleavable linkers, and, indeed, no mention of a cleavable linker in the first place, the cited reference fails to provide the requisite motivation or suggestion to modify the teaching of Patrone et al.

3. Reasonable Expectation of Success

Third, Patrone et al. fail to provide the requisite reasonable expectation of success to include a cleavable linker in biotin ribonucleotide or the matrix.

As pointed out above, the claims require that a cleavable linker is included either between the biotin and ribonucletide or in the solid matrix. Further, the claims require including a step of cleaving the biotin-16-UTP at the cleavable linker. Patrone fails to disclose, suggest, or hint at this limitation. Since Patrone et al. fail to even hint at this limitation, Patrone et al. therefore also fail to provide any possibility that one of ordinary skill in the art could reasonably expect to succeed in including a cleavable linker. The reference thus fails to provide the requisite reasonable expectation of success in modifying the teachings of Patrone et al.

Since Patrone et al. fail to teach every claim limitation, provide a motivation or suggestion to modify the methods, and provide a reasonable expectation of success in modifying the methods, the Patrone reference fails to render the claims obvious under 35 U.S.C. §103.

Applicants respectfully request that this ground for rejection be withdrawn.

Information Disclosure Statement

Applicants have included an information disclosure statement. The Information Disclosure Statement is included under 37 CFR 1.97(c)(2), including the fee set forth under 37 CFR §1.17(p).

Conclusion

In light of the above amendments and remarks, Applicant believes that this case is now in condition for allowance. Should there be any remaining issues that remain unresolved, the Examiner is encouraged to telephone the undersigned.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **546322000100**. However,

the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: April 21, 2003

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